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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	PAPER NUMBER
1636	
MAIL DATE	DELIVERY MODE
12/15/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/507,380	ACHIRON ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-8,10-17 and 22-35* is/are pending in the application.

4a) Of the above claim(s) *5-8,10-12,16,17 and 22-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4 and 13-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 September 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Exhibits A and B, and petititon decision*.

DETAILED ACTION

This action is in response to the amendment, filed 8/19/2008, in which claims 2-3, 9, 18-21 and 36-113 were canceled, and claims 1 and 4 were amended. Claims 1, 4-8, 10-17 and 22-35 are pending.

Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

Election/Restrictions

Applicant's election without traverse of Group I in the reply filed on 11/27/2007 is acknowledged. Applicant's election without traverse of species (A) detection of nucleic acid (claim 13), and (B) all of the genes in Table II (claim 9) in the reply filed on 11/27/2007 is acknowledged.

Claims 5-8, 10-12, 16, 17 and 22-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/27/2007. Applicant indicated that claims 1-4, 9, 13-21, 26-29 and 33-35 were readable upon the elected species. However, claims 16 and 17 are specifically drawn to genes in Table IV, and claims 26-29 & 33-35 are drawn to the combination of genes that is each of the genes in Tables I, II, III, IV and V. Thus, claims 16, 17, 26-29 and 33-35 are not readable upon the elected combination of genes, which is all of the genes in Table II.

Claims 1, 4 and 13-15 are under consideration.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/365,800, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The specification of Application No. 60/365,800 does not describe the genes that show a substantial or significant difference in expression between a subject with multiple sclerosis and a normal, healthy individual. The specification of the 60/365,800 application describes genes that are differentially expressed between subjects with relapse of multiple sclerosis and remission of multiple sclerosis. The specification of the 60/365,800 application does not describe the genes of instant Tables I or II, for example. Thus, the specification does not provide adequate support or enablement for the claimed method of diagnosing a subject with multiple sclerosis, the method comprising determining a level of

expression of at least one gene from Tables I-V, wherein said level of expression is compared to a normal level of expression, especially for the elected combination of genes, which is all the genes listed in Table II.

Claims 1, 4 and 13-15 have an effective filing date of 3/13/2003, which is the filing date of PCT/IL03/00208.

Specification

The substitute specification filed 8/19/2008 has been entered.

The substitute specification filed 8/19/2008 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: sequences added to the specification for which the entire sequence described by the GenBank Accession number is not provided and/or the GenBank Accession number is not sufficient to uniquely identify the sequence incorporated.

For example, the prior art teaches two different sequences for GenBank Accession No. AB002344 (e.g., Table II, SEQ ID NO: 1254). See Exhibit A, which indicates two different GI numbers (i.e. two different sequences for AB002344) existed prior to the effective filing date of the instant application (3/13/2003). The sequence provided in SEQ ID NO: 1254 is 318 nucleotides in length. In contrast, GenBank Accession No. AB002344.1 (GI: 2280479) is 6121 nucleotides in length, and GenBank Accession No. AB002344.2 (GI: 20521008) is 6698 nucleotides in length. Accordingly, the sequence provided in SEQ ID NO: 1254 is not an

insertion of the sequence uniquely identified by GenBank Accession No. AB002344, because it is not identical to the sequence provided in the GenBank entry. Furthermore, the sequence provided in SEQ ID NO: 1254 is not an insertion of a sequence uniquely identified by GenBank Accession No. AB002344, because reference to "AB002344" does not uniquely identify the document to be incorporated by reference. The entry in the table does not specifically refer to the sequence of version 1 or 2 of the sequence (i.e., AB002344.1 (GI: 2280479), October 2001; or AB002344.2 (GI: 20521008), May 2002). Another example is provided by GenBank Accession No. AL021707, which is only referred by GenBank Accession number in the Table and not by a symbol name. Prior to the filing of the instant application, more than one sequence was available for this GenBank entry, which is of a chromosome 22 clone in excess of 100000 nucleotides in length (see the GenBank entries for AL021707 (GI: 2832710), February 1998, page 1 only; and AL021707 (GI: 3204469), June 1998, page 1 only). The specification has been amended to insert a sequence (SEQ ID NO: 1338) for this entry, yet the sequence inserted into the specification is only 474 nucleotides in length.

Applicant is required to cancel the new matter in the reply to this Office Action.

The disclosure is objected to because of the following informalities:

(i) The specification refers to Table V as containing markers that are distinct between disease-related and non-disease related T-cell myelin reactivity (i.e., differential gene expression in MOG-reactive T-cells MS vs. Healthy). See page 49, line 12; and page 50, line 12. These genes are presented in Table IV and not Table V. Table V contains genes described as specific for "probable" MS.

(ii) In the brief description of the drawings, the specification refers to colors that cannot be seen in the black and white drawings. For example, Figures 1A-B, 2A-B and 4 refer to red, green, blue and yellow portions of the drawings.

Appropriate correction is required.

It is noted that color photographs and color drawings are acceptable only for examination purposes if a petition filed under 37 CFR 1.84(a)(2) is granted permitting their use as acceptable drawings. In the event that applicant wishes to use color photographs as acceptable drawings, a petition must be filed for acceptance of the color photographs or color drawings as acceptable drawings. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), three sets of color drawings or color photographs, as appropriate, and, unless already present, an amendment to include the following language as the first paragraph of the brief description of the drawings section of the specification: See 37 C.F.R. 1.121

> The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

Color photographs will be accepted if all conditions for accepting color drawings have been satisfied.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See page 29, line 17; page 31, line 11.

The attempt to incorporate subject matter into this application by reference GenBank Accession numbers is ineffective because the specification attempts to incorporate gene sequences identified as entries in an electronic database (page 115, lines 3-8). The attempt to incorporate subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See 37 CFR 1.57(d) and MPEP § 608.01(p), paragraph I regarding incorporation by reference.

The incorporation by reference will not be effective until correction is made to comply with 37 CFR 1.57(b), (c), or (d). If the incorporated material is relied upon to meet any outstanding objection, rejection, or other requirement imposed by the Office, the correction must be made within any time period set by the Office for responding to the objection, rejection, or other requirement for the incorporation to be effective. Compliance will not be held in abeyance with respect to responding to the objection, rejection, or other requirement for the incorporation to be effective. In no case may the correction be made later than the close of prosecution as defined in 37 CFR 1.114(b), or abandonment of the application, whichever occurs earlier.

Any correction inserting material by amendment that was previously incorporated by reference must be accompanied by a statement that the material being inserted is the material incorporated by reference and the amendment contains no new matter. 37 CFR 1.57(f).

The use of the trademarks GENECHIP (page 16, line 2; page 19, line 9; page 30, lines 15 and 28; page 38, line 16; page 39, line 2), and GENBANK (page 21, lines 5-26; page 115, line 4) has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Response to Arguments - Specification

With respect to the objections to the specification, Applicant's arguments filed 8/19/2008 have been fully considered but they are not persuasive. The response points to the substitute specification, filed 8/19/2008, and to amendments to the substitute specification, also filed 8/19/2008. The substitute specification has been entered; however the amendments to the specification are not in compliance with 37 CFR 1.121 and have not been entered.

The amendment to the specification filed on 8/19/2008 does not comply with the requirements of 37 CFR 1.121(b) because it does not provide an instruction, which unambiguously identifies the location, to delete one or more paragraphs of the specification, replace a paragraph with one or more replacement paragraphs, or add one or more paragraphs. The locations provided in the specification are relative to the originally filed specification and not the substitute specification, which has been entered. The amendment has not been entered. Thus, the objections are maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4 and 13-15 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection**.

The claims require determining a level of expression of the genes listed in Table II. In the reply filed 8/19/2008, Table II was amended by providing a substitute specification. The response states that the substitute specification references each sequence by sequence ID number and does not introduce new matter. Prior to the amendment of Table II, the table listed genes identified by GenBank Accession number (column labeled "Identifier"). Some genes were also identified by a gene symbol; however, not all genes listed in the table were provided with a gene symbol. Thus, the GenBank Accession number was the only way to identify all of the genes in Table II. In the substitute specification, filed 8/19/2008, the table was amended to identify the genes by sequence identifier in addition to the GenBank Accession number. However, the inserted sequences are not supported by the disclosed GenBank Accession numbers.

The material inserted into the specification contains new matter. Specifically, the new matter is sequences added to the specification for which the entire sequence described by the GenBank Accession number is not provided and/or the GenBank Accession number is not sufficient to uniquely identify the sequence incorporated.

For example, the prior art teaches two different sequences for GenBank Accession No. AB002344 (e.g., Table II, SEQ ID NO: 1254). See Exhibit A, which indicates two different GI numbers (i.e. two different sequences for AB002344) existed prior to the effective filing date of

the instant application (3/13/2003). The sequence provided in SEQ ID NO: 1254 is 318 nucleotides in length. In contrast, GenBank Accession No. AB002344.1 (GI: 2280479) is 6121 nucleotides in length, and GenBank Accession No. AB002344.2 (GI: 20521008) is 6698 nucleotides in length. Accordingly, the sequence provided in SEQ ID NO: 1254 is not an insertion of the sequence uniquely identified by GenBank Accession No. AB002344, because it is not identical to the sequence provided in the GenBank entry. Furthermore, the sequence provided in SEQ ID NO: 1254 is not an insertion of a sequence uniquely identified by GenBank Accession No. AB002344, because reference to "AB002344" does not uniquely identify the document to be incorporated by reference. The entry in the table does not specifically refer to the sequence of version 1 or 2 of the sequence (i.e., AB002344.1 (GI: 2280479), October 2001; or AB002344.2 (GI: 20521008), May 2002). Another example is provided by GenBank Accession No. AL021707, which is only referred by GenBank Accession number in the Table and not by a symbol name. Prior to the filing of the instant application, more than one sequence was available for this GenBank entry, which is of a chromosome 22 clone in excess of 100000 nucleotides in length (see the GenBank entries for AL021707 (GI: 2832710), February 1998, page 1 only; and AL021707 (GI: 3204469), June 1998, page 1 only). The specification has been amended to insert a sequence (SEQ ID NO: 1338) for this entry, yet the sequence inserted into the specification is only 474 nucleotides in length.

The original specification, drawings and claims were thoroughly reviewed and no support could be found for the amendment to include the sequence listing and sequence identifiers in each of the tables. Accordingly, the amendment is a departure form the specification and claims as originally filed, and the GenBank entries do not provide support for the amendment.

Claims 1, 4 and 13-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection was made in the Office action mailed 2/20/2008 and has been rewritten to address the amendments to the claims in the reply filed 8/19/2008.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The claims are drawn to a method of diagnosing a human subject with multiple sclerosis. Claim 1 is drawn to the method step of determining a level of expression of each of the genes listed in Table I or II (Table II is the elected species) in a sample obtained from the subject, said sample comprising peripheral blood mononuclear cells, wherein a statistically significant difference between expression levels of each of said genes in said sample obtained from said subject and expression levels of each of said genes in a control sample of peripheral blood cells from a non-diseased subject is an indication that the human subject is afflicted with multiple sclerosis. Claim 4 limits the statistically significant difference to a difference at a confidence level of p=0.5 as determined by at least one test selected from the group consisting of a t-test, a TNoM and an INFO score. Claims 13 and 14 limit the detection

step to the detection of a transcribed polynucleotide and mRNA, respectively. Claim 15 limits the detection to detection via a labeled probe which specifically hybridizes with the transcribed polynucleotide or portion thereof. The nature of the invention is complex in that the level of gene expression must reliably classify a subject as having multiple sclerosis or as not having multiple sclerosis.

Breadth of the claims: For the use of peripheral blood mononuclear cells (PBMCs), the specification broadly envisions obtaining these cells from blood or any other tissue that may have PBMCs as an infiltrate (e.g., page 20, lines 19-22). The claims are not limited to the use of samples of peripheral blood mononuclear cells obtained from blood. The claims encompass embodiments where the difference is relative to a single control individual. The claims encompass the use of any control individual and do not require a group of healthy individuals that are sex- and age-matched to the subject. The claims refer to Table II, now contains reference to sequences present in the sequence listing (identified by SEQ ID NO:), and sequences present in the GenBank database, an electronic database subject to change over time (see Exhibit A). The claims are not explicitly limited to the sequences present in the sequence listing, and different sequences are provided by the sequence listing and GenBank entries (e.g., SEQ ID NO: 1254 and GenBank Accession No. AB002344; see the sequences provided in AB002344.1 (GI: 2280479), October 2001; or AB002344.2 (GI: 20521008), May 2002). The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims.

Guidance of the specification and existence of working examples: The specification teaches the identification of a set of genes that are differentially expressed between humans with

multiple sclerosis (MS) and a group of healthy sex- and age-matched controls, where the difference in expression is statistically significant (e.g., Example I). A minimal set of genes that can be used to reliably classify a subject as having or not having MS is disclosed in Table II. A larger set of genes comprising all of the genes recited in Table II is disclosed in Table I. The specification teaches that these differences in gene expression are observed in mRNA isolated from PBMCs obtained from the blood of subjects and controls (e.g., paragraph bridging pages 15-16; page 41, lines 1-22).

The elected species is all of the genes of Table II. The claims encompass the measurement of expression level of all of the genes of Table II by detecting the level of mRNA expression. Thus, the sequences of the genes are critical or essential to the practice of the invention. However, some genes are referred to by only a GenBank Accession number (and not by a gene symbol), and the specification does not contain the sequences of the GenBank Accession numbers, because the inserted sequences are not the same as the sequences of the GenBank Accession numbers. The specification attempts to incorporate this essential subject matter into this application by reference to the GenBank Accession numbers but is ineffective (page 115, lines 3-8). The attempt to incorporate subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See 37 CFR 1.57(d) and MPEP § 608.01(p), paragraph I regarding incorporation by reference. The nucleic acid sequences of the GenBank Accession Nos. disclosed in Table II are critical or essential to the practice of the invention, but not included in the claim(s) are not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). The GenBank Accession numbers refer to entries in an electronic

database which is subject to change over time (see Exhibit A). "Essential material" may be incorporated by reference, but only by way of an incorporation by reference to a U.S. patent or U.S. patent application publication, which patent or patent application publication does not itself incorporate such essential material by reference. In the instant case, the claims are, in effect, incorporating the sequence of the GenBank Accession numbers by reference to the entries in the electronic database. "While the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in such details, including proportions and techniques, where necessary, as to enable those persons skilled in the art to make and utilize the invention." See MPEP 608.01(p). Accordingly, the reference to the GenBank Accession numbers does not provide the features that are critical or essential to the practice of the claimed invention. For those genes that were well known in the art at the time the invention was made and where the gene name is sufficient to identify the specific sequence of the transcript and protein which is to be used in the step of "determining a level of gene expression," the nucleic acid and amino acid sequences need not be explicitly disclosed in the specification.

Predictability and state of the art: The art teaches that gene expression analysis is commonly used for three different purposes: (1) as a screening tool to identify individual genes of interest that might contribute to an important biological function, (2) to obtain insight into an important biological function, and (3) as a classification tool to sort cases into clinically important categories (Pusztai and Hess, Annals of Oncology, Vol. 15, pages 1731-1737, 2004, cited in a prior action; e.g., paragraph bridging pages 1732-1733). The prior art reveals that differences in gene expression observed between two groups are do not necessarily provide markers that can be used to reliably classify a subject. Golub et al (Science, Bol. 286, pages 531-

537, October 1999, cited in a prior action) teach the use of a two-step procedure to test the validity of gene expression levels as predictors: step 1 involves cross-validation of the predictors on the initial data set, where one withholds a samples, builds a predictor based only on the remaining samples and predicts the class of the withheld sample; step 2 involves the repetition of assessing the clinical accuracy of the predictor set on an independent set of samples (e.g., page 532, right column). Although Golub et al could detect gene expression differences between chemotherapy responders and non-responders, those differences could not be use to predictably classify individuals (e.g., page 533, paragraph bridging left and middle columns). In the instant case, the specification uses gene expression analysis to classify an individual as having or not having MS, where the smallest set of genes disclosed as having this discriminating capability is the set of genes listed in Table II.

Further, Shalon et al (US 2001/0051344 A1, Dec 13, 2001, cited in a prior action) teach that due to variations in genetic make-up of unrelated individuals in a heterogeneous society, differences in the expression of a gene between any two individuals may or may not be significant (e.g., paragraph [0155]). Shalon et al further teach that the larger the number of individuals tested, the more significant the remaining differences in gene expression become and samples from at least 5 and preferably 20-50 different test individuals are assayed to obtain statistically meaningful data showing a statistical elevation or reduction in report levels when compared to control levels (e.g., paragraph [0156]). Pusztai and Hess teach that larger samples sizes may be needed to validate classification tests, and the number of samples will vary depending upon the acceptable error rates, level of inter-patient variability, the size of the difference in mean expression values, and the prevalence of the phenotype among the group

being tested (e.g., page 1734, paragraph bridging columns; Table 1). The specification does not teach the diagnosis of an individual where only one individual is used as a normal, healthy, non-diseased control. The specification teaches the use of a group of age- and sex-matched control subjects. It would be unpredictable to carry out the claimed invention with a single healthy control subject, due to the differences in gene expression that may occur between two individuals by chance and which may not accurately diagnose the test subject.

Amount of experimentation necessary: One would be required to perform a large amount of experimentation to determine if the test could be preformed with a single control subject. Moreover, one would be required to identify tissues other than PBMC isolated from blood for which the level of expression of any combination of genes, including all the genes in Table II, would be diagnostic for MS in humans and other animals, as encompassed by the claims.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claims 1, 4 and 13-15 are not considered to be enabled by the instant specification.

Response to Arguments - 35 USC § 112

With respect to the rejection of claims 1, 4 and 13-15 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, Applicant's arguments filed 8/19/2008 have been fully considered but they are not persuasive.

The response notes that the claims have been amended to limit the method to samples comprising peripheral blood mononuclear cells, each of the genes in Table I or II, human

subjects, and the difference being a statistically significant difference. The response states that the method as claimed has sufficient predictability such that the number of controls need not be increased beyond a single control subject from a non-diseased subject. Moreover, the response asserts that sequences for the claimed genes have been provided in the sequence listing and tables such that it is possible to correlate the sequence of the sequence listing with a particular gene.

These arguments are not found persuasive. The amendments to the claims do not narrow the scope of the claimed invention such that it is predictable. The specification envisions the use of peripheral blood mononuclear cells (PBMCs) obtained from blood or any other tissue that may have PBMCs as an infiltrate (e.g., page 20, lines 19-22). Thus, the claims encompass the comparison of gene expression from PBMCs of different sources in the test subject and control subject. Further, the specification teaches that the gene expression was predictive for PBMC obtained from blood (e.g., paragraph bridging pages 15-16; page 41, lines 1-22). The specification does not teach the expression levels for the genes in PBMCs obtained from any other tissue. Given the teachings in the prior art that gene expression differences between any two individuals are unpredictable (Shalon et al, US 2001/0051344 A1, Dec 13, 2001, paragraph [0155]), it would be unpredictable to compare the expression levels of a single test individual to a single control individual. Differences in gene expression that may occur between two individuals by chance will not provide a reliable basis for diagnosis. The specification teaches the comparison of gene expression levels for each gene in a test subject to the geometric mean of age-matched controls (e.g., paragraph bridging pages 15-16; page 38, lines 22-26; page 39, lines 3-5). Furthermore, the sequences provided in the sequence listing are not the same sequences

incorporated by reference. For example, GenBank AL021707 is directed to a nucleotide sequence greater than 100000 nucleotides in length, yet the specification has been amended to insert a sequence (SEQ ID NO: 1338) for this entry, which is only 474 nucleotides in length. The addition of these new sequences, which are not supported by the original disclosure, does not overcome the deficiencies with regard to the need to know the identity of the sequences in order to perform the claimed method. The claimed sequences are essential to the practice of the method.

Applicant notes that the claims have been amended to remove the reference to Tables III-V. The Examiner's comments regarding these Tables has been removed from the rejection in light of the amendment.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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